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Mini review

Current knowledge on alleviating *Helicobacter pylori* infections through the use of some commonly known natural products: bench to bedside

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ABSTRACT

Helicobacter pylori, a spiral-shaped Gram-negative bacterium, has been classified as a class I carcinogen by the World Health Organization and recognized as the causative agent for peptic ulcers, duodenal ulcer, gastritis, mucosa-associated lymphoid tissue lymphomas, and gastric cancer. Owing to their alarming rate of drug resistance, eradication of *H. pylori* remains a global challenge. Triple therapy consisting of a proton pump inhibitor, clarithromycin, and either amoxicillin or metronidazole, is generally the recommended standard for the treatment of *H. pylori* infection. Complementary and alternative medicines have a long history in the treatment of gastrointestinal ailments and various compounds has been tested for anti-*H. pylori* activity both *in vitro* and *in vivo*; however, their successful use in human clinical trials is sporadic. Hence, the aim of this review is to analyze the role of some well-known natural products that have been tested in clinical trials in preventing, altering, or treating *H. pylori* infections. Whereas some *in vitro* and *in vivo* studies in the literature have demonstrated the successful use of a few potential natural products for the treatment of *H. pylori*-related infections, others indicate a need to consider natural products, with or without triple therapy, as a useful alternative in treating *H. pylori*-related infections. Thus, the reported mechanisms include killing of *H. pylori* urease inhibition, induction of bacterial cell damage, and immunomodulatory effect on the host immune system. Furthermore, both *in vitro* and *in vivo* studies have demonstrated the successful use of some potential natural products for the treatment of *H. pylori*-related infections. Nevertheless, the routine prescription of potential complementary and alternative medicines continues to be restrained, and evidence on the safety and efficacy of the active compounds remains a subject of ongoing debate.

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1. Introduction

The relationship between *Helicobacter pylori* and gastric pathology was described about 30 years ago by Warren and Marshall.[1] Since then, *H. pylori* has been recognized as the causative agent for peptic ulcers, duodenal ulcer, gastritis, dyspepsia, mucosa-associated lymphoid tissue lymphomas, and gastric cancer. Although numerous natural products are used in traditional medicine for the treatment of bacterial infections, the first report on the anti-*H. pylori* activity of plant products was published only 8 years after its discovery.[2] Since then, the anti-*H. pylori* activity of different plant products or extracts has been rigorously tested both *in vitro* and *in vivo* in animal models. Triple therapy, which comprises two antibiotics and a proton pump inhibitor, is a conventionally effective treatment for *H. pylori* infections. However, the prolonged use of these antibiotics can lead to antibiotic resistance in the infectious organisms and also alter the normal biota of the gastrointestinal system. Use of alternative medicines has been reported to alleviate the problems of antibiotic resistance while effectively eliminating the pathogens. There are several available reports on the anti-*H. pylori* activity of natural products in certain databases of academic journals such as PubMed and Scopus, but paradoxically only a few articles are available based on the clinical reports. On mining the list of available clinical reports, it was surprising to observe that most of the natural products that have been extensively reported in *in vitro* or *in vivo* systems were not scaled up to clinical trials and offered no clue on their safety profiles. Although natural products are generally considered safe under some permitted dosage rates, their use can be considered as a dietary supplement or an additive therapy. This review was undertaken to assess several selected natural products (Fig. 1) exhibiting anti-*H. pylori* activity, which have been tested in preclinical and clinical trials.

Table 1 – PubMed

Keywords used for search with article type as clinical trial	Number of articles
(*Helicobacter pylori*)	2935
(*Helicobacter pylori*) AND herb	1
(*Helicobacter pylori*) AND plant	45
(*Helicobacter pylori*) AND extract	9
(*Helicobacter pylori*) AND (complementary medicine)	27
(*Helicobacter pylori*) AND (traditional medicine)	12
(*Helicobacter pylori*) AND (folk medicine)	12
(*Helicobacter pylori*) AND (oriental medicine)	3
(*Helicobacter pylori*) AND [herb OR plant OR extract OR (complementary medicine) OR (traditional medicine) OR (folk medicine) OR (oriental medicine)]	68

2. Search strategy

Because our focus for this review article is to look for the natural products that were tested at clinical settings for anti-*H. pylori* activity, our initial search was made in the PubMed and Scopus databases and restricted to "clinical trials" alone. While searching in the PubMed, we included the option "clinical trial" in the search as PubMed allows restricting the search based on article types. However, this option is not available with Scopus, and hence the term "clinical trial" was included in the keyword. The search was done considering the different terminologies that have been used in the literature for the study on natural products, and the details of search criteria and the outcome of the search in PubMed and Scopus databases are summarized in Tables 1 and 2, respectively. On careful analysis of the "clinical trial" report in both PubMed and Scopus databases, we found that only olive oil, *Nigella sativa* or caraway, mastic gum, broccoli, cranberry, *Prunus mume*, cinnamon, propolis, and curcumin were suitable for this review as these were tested at *in vitro* or *in vivo* level and

Fig. 1 – Commonly known natural products – bench to bedside.

Table 2 – Scopus

Keywords used for search	Number of articles
[TITLE-ABS-KEY("helicobacter pylori") AND TITLE-ABS-KEY("clinical trial")]	5392
[TITLE-ABS-KEY("helicobacter pylori") AND TITLE-ABS-KEY("clinical trial") AND TITLE-ABS-KEY(herb)]	8
[TITLE-ABS-KEY("helicobacter pylori") AND TITLE-ABS-KEY("clinical trial") AND TITLE-ABS-KEY(plant)]	78
[TITLE-ABS-KEY("helicobacter pylori") AND TITLE-ABS-KEY("clinical trial") AND TITLE-ABS-KEY(extract)]	105
[TITLE-ABS-KEY("helicobacter pylori") AND TITLE-ABS-KEY("clinical trial") AND TITLE-ABS-KEY (complementary medicine)]	8
[TITLE-ABS-KEY("helicobacter pylori") AND TITLE-ABS-KEY("clinical trial") AND TITLE-ABS-KEY (traditional medicine)]	23
[TITLE-ABS-KEY("helicobacter pylori") AND TITLE-ABS-KEY("clinical trial") AND TITLE-ABS-KEY (folk medicine)]	2
[TITLE-ABS-KEY("helicobacter pylori") AND TITLE-ABS-KEY("clinical trial") AND TITLE-ABS-KEY (oriental medicine)]	0
[TITLE-ABS-KEY("helicobacter pylori") AND TITLE-ABS-KEY("clinical trial") AND TITLE-ABS-KEY(herb) OR TITLE-ABS-KEY(plant) OR TITLE-ABS-KEY(extract) OR TITLE-ABS-KEY("complimentary medicine") OR TITLE-ABS-KEY("traditional medicine") OR TITLE-ABS-KEY("folk medicine") OR TITLE-ABS-KEY("oriental medicine")]	134

also at clinical conditions. Although a few others, such as peppermint oil and Chinese herbal medicine, have been reported in clinical trials, they were excluded from this review either for the reason that the articles are not available in the English language or the data were found to be inappropriate or unsuitable for the current review.

3. Olive oil

Olive oil is produced by pressing whole olives, and is commonly used in cooking, cosmetics, pharmaceuticals, and soaps. Romero et al[3] examined the effect of olive oil on eight different *H. pylori* clinical isolates, including three antibiotic-resistant strains, and observed the potent anti-*H. pylori* activity of olive oil against all the tested strains. In addition to the antibacterial activity, it is also worth noting that the active phenolic compounds in olive oil can remain stable for several hours under harsh acidic environments. Among the various phenolic compounds tested, the dialdehydic form of decarboxymethyl ligstroside aglycone showed the strongest bactericidal effect at a very low concentration of 1.3 μg/mL. Contrary to the findings of Romero et al,[3] Preuss et al[4] reported that olive oil does not exert antibacterial effect against *H. pylori*; this conflicting finding could be attributable to the difference in the use of olive oil, which was used only as a carrier for other herbal oils and not as the principal component in the study of Preuss et al.[4]

Based on the results of previous studies, Castro et al[5] performed two different pilot clinical studies comprising 30 participants, identified as *H. pylori*-positive, per trial. In the first trial, all 30 individuals received 30 g of olive oil at two different time intervals—initially, washed virgin olive oil was administered for 14 days and then, after a 1-month gap, unwashed virgin olive oil was administered for 14 days. The researchers found that *H. pylori* infection was eliminated in eight of the 30 (27%) individuals after 4–6 weeks from the first clinical intervention, and at the end of the study, 12 of the 30 individuals did not show *H. pylori* infection. This result indicates that olive oil had cleared the *H. pylori* infection in 40% of the cases on completion of the treatment protocol. In the second clinical intervention, 30 g of different virgin olive oils was administered for 14 days to 30 *H. pylori*-positive individuals. Only three of the 30 (10%) individuals were *H. pylori*-negative after 4–6 weeks, and five of the 30 individuals (11%) were negative in 24–72 hours after administration of the last oil dose.[5]

The results of the two above-mentioned interventions indicate that although virgin olive oil could exert appreciable anti-*H. pylori* activity *in vitro*, it only showed a moderate effectiveness in eradicating *H. pylori* in clinical settings. However, further appropriate clinical studies, particularly with longer periods, different administration conditions, and different types of olive oils, are required to verify these findings.

4. *Nigella Sativa* or black caraway

The seeds of *N. sativa*, an annual flowering plant native to the south and southwest Asia, have been valued for their healing properties since time immemorial.[6] Many active ingredients isolated from *N. sativa* have been shown to exhibit various pharmacological effects such as immune stimulation, anti-inflammatory, anticancer, and antimicrobial activities. The antibacterial activity of the phenolic fraction of *N. sativa* oil was first reported by Toppozada et al.[7] However, its activity against *H. pylori* was described only 40 years later (in 2005) by O'Mahony et al,[8] who found that the hot aqueous extract of *N. sativa* exerted 100% bactericidal activity against *H. pylori* when tested against a standard American Type Culture Collection strain and six different clinical isolates. Nevertheless, the minimum bactericidal concentration (MBC) was not reported in that study because only one concentration of the direct aqueous extract was used. Later, Zaidi et al[9] examined the activity of *N. sativa* by using seven *H. pylori* clinical isolates and different concentrations of 70% alcoholic extract of *N. sativa* (7.8 μg/mL, 15.6 μg/mL, 31.2 μg/mL, 62.5 μg/mL, 125 μg/mL, 250 μg/mL, and 500 μg/mL). It was demonstrated that the extracts of *N. sativa* completely inhibited the growth of *H. pylori* at 500 μg/mL, and that the MBC was 62.5 μg/mL against six isolates and 125 μg/mL against one isolate. Furthermore, Hajimahmoodi et al[10] tested the methanolic extract of *N. sativa* against 12 clinical isolates of *H. pylori* and found that the minimum inhibitory concentration (MIC) against three, eight, and one isolates was 128 μg/mL, 256 μg/mL, and 512 μg/mL, respectively. This difference in the inhibitory concentrations among these three above-mentioned studies might be attributable to the difference in the solvent used and the extraction procedure used. Nevertheless, despite this varying MBC or MIC, it is clear that *N. sativa* exerts an appreciable anti-*H. pylori* activity, and therefore, can be considered for testing in human volunteers.

Different active components of *N. sativa* have been reported to exhibit potent activity against *H. pylori*-associated infections, although they have not been tested in the *H. pylori* infection model. The alcoholic extract of *N. sativa* was observed to show potent antiulcer activity in two different ulcer models such as pyloric ligation and aspirin-induced gastric mucosal damage.[11] In addition, *N. sativa* oil was proposed to exert a hypogastrinemic effect by activating guanylate cyclase, leading to an increased intracellular cGMP and a subsequent decrease in intracellular Ca^{2+}, and gastrin secretion.[12] Furthermore, thymoquinone, an active ingredient isolated from *N. sativa*, was reported to exhibit antioxidant, anti-inflammatory, and anticancer activities.[13] As *H. pylori* infection can lead to ulcer, inflammation, and gastric cancer, treatment using *N. sativa* may result in the eradication of *H. pylori* infection as well as the disease caused by the organism.

Salem et al[14] tested the efficacy of *N. sativa* seeds against *H. pylori* infection in 88 patients with nonulcer dyspepsia, and compared it with that of standard triple therapy. It was observed that *N. sativa*, administered as 500-mg capsules containing ground *N. sativa* seeds, eradicated *H. pylori* infection. The eradication rates achieved by triple therapy, 1 g, 2 g, and 3 g of *N. sativa* were 82.6%, 47.6%, 66.7%, and 47.8%, respectively, and no statistically significant difference was observed between the eradication rates achieved using triple therapy and 2 g of *N. sativa*. However, the study did not explain about the lesser efficacy of *N. sativa* at higher doses. In a comment on their own article in *Alimentary Pharmacology & Therapeutics*,[15] May et al[16] indicated that they had observed an interpretable difference in the treatment outcome between the *H. pylori*-positive and -negative patients when treated with a fixed combination of 90 mg of peppermint oil and 50 mg of caraway oil. However, the drawback in their study was that only 25% of the patients (24 out of 96) were *H. pylori* positive and the remaining 75% of the patients were *H. pylori* negative, thus necessitating a study with a larger population to prove its effectiveness. Furthermore, in their study, caraway oil was used in combination with peppermint oil, and hence, the clear role of caraway was not completely proven because peppermint oil was also noted to exhibit anti-*H. pylori* activity.

5. Mastic gum

Mastic gum is a natural resin that is excreted from the trunk and branches of the mastic bush (*Pistacia lentiscus*). Huwez et al[17] were the first to report on the bactericidal effect of mastic gum against *H. pylori*, and observed that crude mastic gum could kill *H. pylori* at a concentration of 0.06 mg/mL, regardless of whether the organism was sensitive or resistant to metronidazole. In addition, they also reported that the lowest concentration tested, 0.0075 mg/mL, could significantly inhibit the growth of *H. pylori*. This report was followed by a study by Marone et al,[18] who found that 50% and 90% of *H. pylori* strains were inhibited at a mastic gum concentration of 125 μg/mL and 500 μg/mL, respectively. In addition, the morphological changes assessed through transmission electron microscopy were also reported, and it was noted that at a sub-MBC concentration, blebbing, morphological abnormalities, and cellular fragmentation were observed. These studies were further validated by Loughlin et al[19] through *in vitro* susceptibility testing and *in vivo H. pylori* eradication using specific-pathogen-free CD1 mice infected with *H. pylori*. In accordance with the previous reports, Loughlin et al[19] found that mastic gum exhibited good MIC and MBC against *H. pylori* SS1, with values of 7.80 mg/L and 31.25 mg/L, respectively. However, paradoxically, mastic gum failed to eradicate *H. pylori* infection in the infected mice model and did not produce any reduction in the bacterial load, although the mouse stomach was immediately examined after 7 days of treatment. The same year, Bebb et al[20] reported the role of mastic gum in *H. pylori* eradication in nine patients with *H. pylori* infection and proved the inefficiency of mastic gum in clearing *H. pylori* infections. In their study, mastic gum was administered at a high dose of 1 g four times a day for 14 days, and at the end of the treatment regime, all patients were still found to be *H. pylori* positive.

Regardless of the contradictory reports on the activity of mastic gum, research on its anti-*H. pylori* activity has continued. For instance, Paraschos et al[21] performed both *in vivo* and *in vitro* assays of the anti-*H. pylori* activity of mastic gum. Their study differed from the previous studies in that the treatment regime used was longer (3 months, as opposed to 1 week in the study by Loughlin et al[19]) and the insoluble polymers were removed from mastic gum to ameliorate solubility. Administration of mastic gum at a concentration of 0.75 mg/day led to an approximately 30-fold reduction in *H. pylori* colonization in the infected mice; however, this eradication did not attenuate chronic inflammatory infiltration and chronic gastritis. Furthermore, the acidic and neutral fractions of mastic gum were tested for anti-*H. pylori* activity *in vitro*, and it was found that the acid fraction was the most active (MBC = 0.139 mg/mL) and that isomasticadienolic acid was the most active isolated compound (MBC = 0.202 mg/mL). These results show that administration of mastic gum may be effective in reducing *H. pylori* colonization, and that the major triterpenic acids in the acidic fraction may be responsible for such an activity. In another study, Dabos et al[22] administered two different doses of mastic gum (350 mg and 1.0 g) three times a day for 14 days, and noted that the *H. pylori* was eliminated at a rate of 30.8% and 38.5%, respectively. However, the authors had used only a small sample size ($n = 13$ participants) and did not include a detailed description of the difference between their study and the report by Bebb et al.[20]

6. Broccoli

Broccoli is an edible green plant in the cabbage family, whose large flower head is used as a vegetable. Fahey et al[23] isolated sulforaphane, a glucosinolate precursor, from broccoli and broccoli sprouts, and showed that the isolated compound was effective against three reference strains and 45 clinical isolates of *H. pylori* with an MIC of <4 μg/mL for 90% of the strains. In addition, the experiment was also performed at different pH levels, and it was observed that the MIC remained unaltered at the neutral pH and at a pH of 5.8. As the pH of 5.8 closely reflects the gastric juxta mucosal pH, it can be concluded that sulforaphane could retain the *in vivo* biological activity against *H. pylori*. Furthermore, the bactericidal activity of sulforaphane

was also confirmed by briefly exposing the human epithelial cell line (HEp-2) infected with *H. pylori* to sulforaphane. In complementary experiments, sulforaphane concentration five times higher than the MIC was found to kill all the intracellular *H. pylori* in forestomach tumors in ICR mice in 4–8 hours. Moreover, sulforaphane was noted to possess antioxidative, anti-inflammatory, and anticancer activities,[24] and was also reported to inhibit urease activity.[23] Later, Moon et al[25] performed a study to determine the anti-*H. pylori* activity by using chloroform, methanol, ethylacetate, butanol, and water extracts. Among the different extracts tested, the methanolic extract exerted the most potent anti-*H. pylori* activity (as compared to ethyl acetate and butanol extracts), whereas the aqueous extract did not produce any activity. The anti-*H. pylori* activity of the extracts was observed to be in the following order: chloroform > hexane > ethyl acetate > butanol > crude methanol extracts.

A pilot study conducted by Galan et al[26] using nine patients revealed that *H. pylori* was eradicated in 33.33% of the patients who consumed broccoli sprouts at a dose of 14 g, 28 g, or 56 g twice a day for 7 days. When a stool antigen test was conducted, it was found that at the end of 7 days, seven out of 9 patients (78%) remained *H. pylori* negative; however, at the end of the 35th day, six out of nine patients (67%) were *H. pylori* negative, indicating that there is a chance of recurrence to infection. Furthermore, immunostaining for the detection of *H. pylori* in the biopsy taken from these patients indicated that only three out of nine patients were completely negative for *H. pylori*, exhibiting *H. pylori* eradication in 33% of the cases. In another study, the participants were made to consume 10 servings of 130 g of fresh juvenile broccoli tips to determine its anti-*H. pylori* activity.[27] The urea broth test carried out prior to and after consumption indicated no difference, suggesting no activity against *H. pylori*. However, a major drawback of this study was that only five volunteers received broccoli for only a short period of 3 days.

Similar results were also observed by Yanaka et al,[28] who screened *H. pylori* stool antigen after administering 70 g of broccoli sprouts/day containing 420 μmol of Sulforaphane precursor to participants for 8 weeks and found that 32% (8 of 25) of the participants were *H. pylori* negative at 8 weeks. However, most of the participants were noted to be positive for *H. pylori* after 6 months of intervention, whereas two participants were negative for *H. pylori*, thus indicating that broccoli sprout treatment reduced *H. pylori* colonization, but did not completely eradicate *H. pylori*.[28] In the same study, broccoli sprouts were homogenized and administered to C57BL/6 mice (~3 μmol/mouse/day of glucoraphanin equivalents), which resulted in decreased corpus gastritis and protected the mice from gastric mucosal inflammation. This finding suggests that sulforaphane may not only have a direct antibacterial effect on *H. pylori* colonization, but its primary effect may also be via the upregulation of the host's systemic protection against oxidative stress and inflammation, resulting in an initial decrease in *H. pylori* colonization.

Although varying results have been reported, it is worth noting that sulforaphane has been found to exert a potent anti-*H. pylori* activity and inhibit *H. pylori* urease, along with antioxidative, anti-inflammatory, and anticancer activities. Hence, instead of administering alone, testing this isolated compound in combination may be beneficial in obtaining more convincing results in clinical settings. Furthermore, although all the results are not completely justifiable to conclude that broccoli consumption has therapeutic benefit, the available studies underline that regular consumption of broccoli could improve the endurance of the gastrointestinal system against *H. pylori*-like infections.

7. Cranberry

Cranberries consist of nearly 90% water and are a great source of dietary flavonoids, including anthocyanins and proanthocyanins with high antioxidant potential and well-documented health benefits.[29] Zhang et al[30] published the first clinical report on the efficacy of consuming cranberry juice in suppressing *H. pylori* infection. In the double-blind, randomized placebo-controlled trial, 97 of the 189 *H. pylori*-positive individuals received 250 mL of cranberry juice and 92 participants received placebo twice a day for 90 days. The efficacy assessed at 45 days and 90 days showed that 14.43% (14 of 97) and 5.44% (5 of 92) of the participants in the cranberry and placebo groups were *H. pylori* negative, respectively. Although 14 participants were found to be *H. pylori* negative at both the intervention points, it is worth noting that only 11 participants commonly remained *H. pylori* negative, indicating that the other three participants might have developed recurrence of infection; thus, the efficacy of cranberry against *H. pylori* infection is questionable. In addition, three participants who were *H. pylori* positive at 35 days were negative at 90 days, suggesting that a longer intervention may also prove effective in eradicating *H. pylori* infection. However, the density and intensity of the bacteria in the gastric mucosa of the 13c-urea-positive individuals were not analyzed, and hence, the actual *H. pylori* status is unclear; however, the biopsy of the stomach and a probable *H. pylori* identification might have provided an added advantage. Furthermore, the study failed to analyze the *H. pylori* status of the participants who were negative for the bacterium after a specific window period, and no subsequent follow-up was carried out to check the *H. pylori* status.

As an alternative to the administration of cranberry as a monotherapy, Shmuely et al[31] conducted a double-blind randomized clinical study to test the additive effect of cranberry juice along with a triple therapy consisting of omeprazole, amoxicillin, and clarithromycin (OAC). The OAC therapy was administered during the 1st week, followed by cranberry administration for 2 weeks, and it was found that 95.2% and 73.9% of the female and male patients were *H. pylori* negative, respectively. However, no significant difference was observed among the male patients when the cranberry–OAC group was compared with the placebo or nonplacebo groups, indicating that the additive therapy was only effective in female patients. In another study testing the additive effect along with *Lactobacillus* sp., it was noted that the intake of lactobacillus or cranberry could reduce *H. pylori* infection in children positive for the bacterium; however, no additional effect was noticed when lactobacillus and cranberry were administered in combination.[32]

Furthermore, Burger et al[33,34] reported the antiadhesive property of a high molecular weight constituent from

cranberry. In their two consecutive studies, it was shown that a high molecular weight constituent from cranberry could interfere with the sialic-acid-specific adhesion of *H. pylori* to gastric mucus. In addition to anti-*H. pylori* activity, Chatterjee et al[35] reported that berry extract could increase the susceptibility of *H. pylori* to the antibiotic clarithromycin. An additive inhibitory effect was noted when clarithromycin was used in combination with different concentrations of the berry extract, thus indicating the potential antibacterial activity of the berry extract used individually or in combination with antibiotics against *H. pylori*. Matsushima et al[36] found that the polyphenolic compounds from cranberry could inhibit *H. pylori* proliferation and induce morphological changes leading to bacteriostatic activity. Nevertheless, although the overall efficacy of cranberry appears to be appreciable, further studies on large populations are warranted to justify its efficacy.[36]

8. *Prunus mume*

P. mume, commonly known as the Chinese plum or Japanese apricot, is related to both the plum and apricot trees. Syringaresinol, an active compound isolated from *P. mume*, was shown to inhibit more than 90% motility of *H. pylori* at a concentration of 500 μg/mL, and exhibited an IC_{50} value of 50 μg/mL. As motility is essential for *H. pylori* migration and colonization, the inhibition of motility will lead to reduced colonization of the bacterium in the gastric mucosa.[37] In a *H. pylori*-infected Mongolian gerbils model, it was observed that consumption of *P. mume* concentrate significantly reduced the urease A expression in the infected stomach, indicating the decrease in *H. pylori* infection.[38] Furthermore, Enomoto et al[39] demonstrated the preventive effect of *P. mume* on chronic atrophic gastritis by inhibiting *H. pylori* infection and reducing active mucosal inflammation. In their study, the volunteers received either dried or pickled *P. meme*, and at the end of the interventional period, histological examination of the biopsy samples from the nonelderly individuals (<65 years) showed that the high-intake group (X3 JA daily) had significantly less *H. pylori* load, neutrophil infiltration, and mononuclear infiltration in the gastric mucosa, when compared with the low-intake group (X3 JA daily).

9. Cinnamon

Cinnamon is a spice obtained from the inner bark of several trees from the genus *Cinnamomum*. Tabak et al[40] reported that ethanolic and methylene chloride extracts of cinnamon could inhibit both *H. pylori* and free urease. In addition, O'Mahony et al[8] demonstrated that cinnamon has bactericidal activities against *H. pylori*; however, the hot aqueous extract of cinnamon used in their study failed to exhibit total inhibition of the bacterial growth. Furthermore, in a controlled trial carried out by Nir et al,[41] it was found that cinnamon extract, as a single agent, at a higher concentration of 80 mg/day (twice daily for 4 weeks) failed to eradicate *H. pylori* infection. However, the study was conducted in a smaller group of volunteers (15 people). Although these findings show that cinnamon extract can be tolerated well without any side effects, they cannot be completely justified owing to the lack of clinical studies in a large population.

10. Propolis

Propolis is a resinous mixture that was collected from tree buds, sap flows, or other botanical sources by honey bees, and it was widely reported to induce biological activities including antibacterial, emollient, immunomodulator, anti-allergic, antioxidant, and anticancer activities.[42] In 1998, Hashimoto et al[43] first reported the anti-*H. pylori* activity of propolis, and later in 2001 Banskota et al[44] reported that labdane-type diterpenes and some of the prenylated phenolic compounds isolated from propolis exhibit anti-*H. pylori* activity. In 2003 and 2005, Boyanova et al[45,46] reported that 30% ethanolic extract of propolis exerted dose-dependent anti-*H. pylori* activity against 38 and 94 different clinical isolates of *H. pylori*, respectively. A similar *in vitro* study by Nostro et al[47,48] showed that propolis has an MIC_{90} value of 0.075 mg/mL, using 11 clinical isolates of *H. pylori*, and in the subsequent year a report from the same group indicated that propolis in combination with the antibiotic clarithromycin also exerted good anti-*H. pylori* activity. Based on these *in vitro* reports, the first clinical report on propolis was described in the study by Coelho et al,[49] where 18 *H. pylori*-positive patents (11 females and 7 males) were orally administered with 20 drops of alcoholic preparation of propolis three times a day for 1 week. Forty days later, the clinical intervention noted that 83% of the patients remained positive for *H. pylori*, leading to the conclusion of the minimal effectiveness of propolis in eliminating *H. pylori* infection in human volunteers.[49] However, this warrants a more detailed study with comparative standard therapy and different doses with longer periods of treatment and the involvement of a larger number of participants. Recently, Cui et al[50] reported that caffeic acid phenethyl ester, an active compound from propolis, can competitively inhibit *H. pylori* peptide deformylase (*Hp*PDF) with an IC_{50} value of 4.02 μM. Because *Hp*PDF catalyzes the removal of the formyl group from the N terminus of nascent polypeptide chains and this process was essential for *H. pylori* survival, inhibiting *Hp*PDF will be effective in anti-*H. pylori* therapy.

11. Curcumin

Curcumin is a diarylheptanoid, and it is the principal curcuminoid of the popular south Asian spice turmeric, which is a member of the Zingiberaceae family. Turmeric's other two curcuminoids are desmethoxycurcumin and bisdesmethoxycurcumin. The curcuminoids are phenolic in nature and responsible for the yellow color of turmeric. When curcumin was tested against 19 strains of *H. pylori*, it inhibited the growth of all strains with an MIC range of 6.25–50 μg/mL.[51] Curcumin was also reported to inhibit shikimate dehydrogenase, an enzyme responsible for the biosynthesis of aromatic amino acids (phenylalanine, tyrosine, and tryptophan) in *H. pylori*. Inhibition of this enzyme is of particular importance in antimicrobial drug therapies, because human beings are not dependent on this enzyme of amino acid synthesis, which

makes the inhibition of shikimate dehydrogenase toxic only to pathogens and not to the host.[52] A study by De et al[53] tested the anti-*H. pylori* activity of curcumin against 65 clinical isolates in *in vitro* and *in vivo* using *H. pylori*-infected C57BL/6 mice model. The *in vitro* results showed that the MIC of curcumin ranged from 5 μg/mL to 50 μg/mL, proving its effectiveness in *H. pylori* inhibition. In mice, curcumin is shown to be highly effective in eradication of *H. pylori* as well as in restoration of *H. pylori*-induced gastric damage.[53] Although various *in vitro* and *in vivo* reports are available on the effectiveness of curcumin against *H. pylori*, only one clinical study using curcumin has described the ineffectiveness of curcumin in eliminating *H. pylori* infection or its associated symptoms. In this study, only 12% (3 out of 25) of the patients were *H. pylori*-negative at the end of the treatment regime using 30 g curcumin for 7 days.[54]

12. Conclusion

Among the published clinical trials obtained from the databases—focusing on *H. pylori* (219), olive oil (138), *N. sativa* (6), mastic gum (1), broccoli (52), cranberry (54), *P. mume* (3), cinnamon (26), propolis (0), and curcumin (1)—it is surprising to note that to date, there have been no registered trials analyzing the activity of these natural products except one on cranberry against *H. pylori*. Although these natural products with proven health benefits have been used since time immemorial for alleviating various gastrointestinal tract diseases, their mechanism of action is not well established. Moreover, studies on the safety and efficacy of the active compounds isolated from these products are extremely important in our ongoing efforts to formulate these compounds and make them available for further clinical use.

Conflicts of interest

All authors declare no conflicts of interest.

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